IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jacobus M. LEMMENS et al	
Serial No.:	10/024,520	Group Art Unit: 1614
Confirm. No.:	2171	Examiner: PULLIAM, Amy
Filed:	December 21, 2001	

For: AMLODIPINE FREE BASE

SUPPLEMENT

SUBMISSION OF EXECUTED 132 DECLARATION

Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

April 16, 2004

Sir:

Further to Request for Continued Examination (RCE) filed on April 5, 2004, wherein applicants submitted the Rule 132 Declaration of Arlette Vanderheijden, Applicants hereby submit the executed version of the Declaration. As the Examiner will note, the text of the Declaration has not changed. Entry and consideration of the Declaration are respectfully requested.

Should the Examiner have any questions regarding this application, she is encouraged to contact Mark R. Buscher (Reg. No. 35,006) at telephone No. 703 753 5256.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jacobus M. LEMMENS *et al.*	:	Examiner: A. PULLIAM
Serial No.:	10/024,520	:	Group: 1615
Filed:	December 21, 2001	:	
For:	AMLODIPINE FREE BASE		

DECLARATION UNDER 37 C.F.R.§ 1.132

I, Ing. Arlette Vanderheijden, do hereby declare as follows:

1. I am an employee of the assignee in the above-identified U.S. patent application.
2. In 1995 I completed my Higher Laboratory Education (Hoger Laboratorium Onderwijs) studies at Hogeschool Heerlen[1], in Sittard, The Netherlands in Organic Chemistry. I earned the title, "Ing." which I believe is equivalent to a Bachelor of Science degree in the U.S.
3. In 1997 I became employed by Synthon BV, the assignee of the present application, and have remained so to the present. I am presently a project manager and part of my responsibilities includes studying amlodipine pharmaceutical compositions.
4. I am aware that the Examiner has rejected the claims in the above-identified patent application over Lazar et al, U.S. Patent 5,155,120 (Lazar) with additional reliance upon Davison et al, U.S. Patent 4,879,303 (Davison). I further understand that the Examiner's position is that Lazar teaches a pharmaceutical composition that contains amlodipine base, albeit the form of the amlodipine base is not described and the clinical studies disclosed therein actually do not use the base but instead use the salt amlodipine benzenesulfonate (see column 3, lines 29-30 of Lazar). Davison mentions a composition containing amlodipine base but does not disclose the form of the base or the manufacture/isolation of the base in solid form.

[1] The School has since changed its name to Hogeschool Zuyd.

5. In order to show that the solid form of the amlodipine base effects the tabletting properties, the following experiments were carried out under my supervision and control.
6. Four samples of amlodipine free base were prepared; namely crystalline amlodipine free base Form I, crystalline amlodipine free base Form II, crystalline amlodipine free base "Form III,"[2] and amorphous amlodipine free base. The preparation of these forms is shown in Appendix A.
7. The amlodipine free base Form II contained large lumps unsuitable for tabletting and was therefore sieved (manually) over an 850 μm Retsch sieve, before blending with the other excipients. The amlodipine free base Form III contained large and hard lumps unsuitable for tabletting and was therefore milled in a Fritsch P14 Pulverisette 0.5 mm sieve, before blending with the other excipients.
8. The amorphous amlodipine free base was incapable of being blended or tabletted as shown in the pictures in Appendix B. Photo 1 shows the yellow, sticky amorphous amlodipine free base that was isolated. Photos 2 and 3 show that the amorphous amlodipine free base does not blend with the excipient in order to form a tablettable blend.
9. The stickiness of tablets using the various forms of amlodipine free base were evaluated using the following tablet formula:

Amlodipine free base	3.67 %
Microcrystalline cellulose	48.2 %
Calcium sulphate dihydrate	48.2 %
Total	100 %

The tablet preparation comprised mixing the amlodipine free base, the microcrystalline cellulose and the calcium sulphate dihydrate in a Bohle VMA 10 high shear blender. The excipients were mixed for 40 minutes at 40 rpm with the chopper off. The powder blend was compressed on a

[2] This sample is crystalline but does not appear to be pure Form I or Form II. For simplicity I refer to it as Form III, although it may not in fact be a different crystalline polymorph.

Korsch EK0 Excenter Press into tablets with 20 mm round flat punches, having a hardness of approximately 250N.

10. After compression of 50 tablets, the tablet punches were removed from the tabletting machine. The tablet material that was sticking to the tablet punches was extracted from the punches using methanol and an ultrasonic bath. This procedure was repeated for runs of 100, 150, 200, 250 and 300 tablets. The extracts together with amlodipine calibration samples were measured spectrometrically, at 237 nm. The amount of amlodipine in the samples was calculated from the calibration curve and the total amount of amlodipine extracted from both the upper and lower punch was plotted against the amount of tablets made. An average value for stickiness was calculated from the slope of the regression line by forcing the y-intercept of the line through zero. The results are summarized below:

Type of Amlodipine Free Base in Tablet	Average Stickiness
Form I	0.07 μg ADP.cm^{-2}.tablet^{-1}
Form II	2.93 μg ADP.cm^{-2}.tablet^{-1}
Form III	0.10 μg ADP.cm^{-2}.tablet^{-1}
Amorphous	Not Capable of Tabletting

11. From the above results and the pictures in Appendix B it is clear to me that crystalline forms of amlodipine free base are much more suitable for making pharmaceutical compositions than an amorphous form, which is totally unsuitable.
12. Lazar and Davison both list Pfizer Inc. as the assignee. Recently a new patent, U.S. 6,680,334 to Bentham et al (Bentham) was issued that also recites Pfizer Inc. as the assignee. Bentham explains that the original Pfizer in-house material was unsuitable for formulating. A crystalline material, preferably one that is "free from amorphous free base" is preferred (See Bentham column 3 lines 19-21). From the disclosure in Bentham, I understand that the original Pfizer amlodipine free base material was at least partially amorphous and that is why the tabletting test

in Davison showed the free base as being sticky to punches. In contrast, crystalline amlodipine free base can be very unsticky, i.e. show good punch release characteristics.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true and further that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

A Vanderheijden
Ing. Arlette Vanderheijden

07-04-2004
Date